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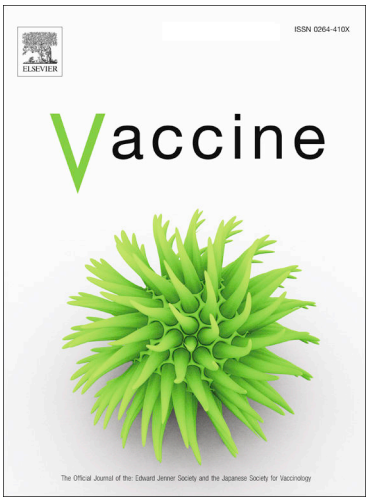

Short communication

Safety surveillance of the NVX-CoV2373 COVID-19 vaccine among Koreans aged 18 years and over

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Safety surveillance of the NVX-CoV2373 COVID-19 vaccine among Koreans aged 18 years and over

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ABSTRACT

Background: In the Republic of Korea (Korea), the NVX-CoV2373 (Novavax) coronavirus disease 2019 (COVID-19) vaccination was administered to 18-year-olds and over from February 14, 2022. This study sought to assess the frequency and severity of reported adverse events following the Novavax COVID-19 vaccination in Korea.

Methods: Adverse events based on two national vaccine safety data were analyzed; the COVID-19 vaccination management system (CVMS) and the text-message survey (TMS).

Results: CVMS identified that the reporting rate of adverse events per 100,000 doses were lower after booster doses (84.0) than after dose 1 (254.6) or dose 2 (272.9); and in 65-year-olds and over (83.4) than

in 18- to 64-year-olds (168.1). The TMS found that local and systemic adverse events were lower in 65-year-olds and over than in 18- to 64-year-olds (p<0.001).

Conclusions: Overall, we identified no major safety issues and fewer adverse events following the Novavax COVID-19 vaccination among 65-year-olds and over in Korea.

Keywords: COVID-19; COVID-19 vaccines; Vaccination; Vaccines; Safety

1. Introduction

In the Republic of Korea (Korea), the Ministry of Food and Drug Safety (MFDS) authorized the NVX-CoV2373 (Novavax) coronavirus disease 2019 (COVID-19) vaccine for primary immunization—two doses with three weeks apart—of persons aged 18 years and over on January 12, 2022 [1]. The Novavax COVID-19 vaccine is a recombinant spike protein nanoparticle vaccine with Matrix-M adjuvant and was shown to be effective to protect against infection with SARS-CoV-2 that causes COVID-19 based on clinical trials [2–5]. Following the World Health Organization (WHO) global recommendations for use and a conclusion by the Korea Advisory Committee on Immunization Practices (KACIP) in 2022 [6–8], the primary series (dose 1 and dose 2) of Novavax COVID-19 vaccine was nationally distributed to persons aged 18 years and over from February 14, 2022, targeting unvaccinated individuals and high-risk groups for severe COVID-19 and death including hospitalized patients, the elderly and severely disabled [9]. Although dose 3 and dose 4 of the Novavax COVID-19 vaccine were initially recommended for the ages of 18 years and over from February 14, 2022, and for the ages of 50 years and over from July 18, 2022, respectively [9–11], booster doses (dose 3 or more) regardless of administration history of dose 3 or dose 4 have become available for persons who received the primary series of COVID-19 vaccines since December 17, 2022 in Korea [12]. Moreover, homologous booster doses of Novavax COVID-19 vaccination are recommended as a standard immunization and persons after the primary series of mRNA- or viral vector-based COVID-19 vaccine can receive booster doses of the Novavax COVID-19 vaccine if they request or due to medical reasons assessed by immunization doctors [9,10]

The Korea Disease Control and Prevention Agency (KDCA) operates the COVID-19 vaccination management system (CVMS, a web-based passive vaccine safety surveillance system) to detect safety signals, monitoring adverse events following immunization (AEFIs) for further evaluation. Doctors and forensic pathologists can report AEFIs to the CVMS regardless of causation between vaccines and events according to the Infectious Disease Control and Prevention Act. In addition, the text-message survey (TMS) is conducted to investigate adverse events and health conditions following COVID-19 vaccination for specific populations who consent to receive text messages through smartphones on the first day of vaccination [13]. This study aimed to assess the frequency and severity of reported adverse events following the Novavax COVID-19 vaccination among 18-year-olds and over in Korea.

2. Methods

2.1. COVID-19 Vaccination Management System

We used data on adverse events after the primary series and booster doses of Novavax COVID-19 vaccination among persons aged 18 years and over reported to the CVMS from February 14 to December

31, 2022. Data on vaccines other than the Novavax COVID-19 vaccine, administered outside of Korea, and before authorization for use were excluded. Adverse events were classified into two types: non-serious and serious events according to the Guidelines for Adverse Events Following COVID-19 Immunization [13]. Non-serious adverse events include common reactions such as redness, pain, and swelling at the injection site, myalgia, fever, headache, chills, and others. Serious adverse events include death, suspected anaphylaxis, adverse events of special interest (AESIs), intensive care unit admission, life-threatening events, permanent disability or sequelae, and others.

2.2. Text-message survey

Text messages were sent to persons aged 18 years and over who received the primary series of the Novavax COVID-19 vaccine to complete daily surveys on days 0 to 7 from February 21 to April 24, 2022. The survey items included questions about experiences of local adverse events (pain, redness, swelling, itching, and urticaria at the injection site) and systemic adverse events (fever or heat, chills, headache, joint pain, myalgia, fatigue or tiredness, nausea, vomiting, diarrhea, abdominal pain, rash, armpit tenderness, chest pain, and dizziness), limits to normal daily activities, and visits to healthcare facilities (emergency room, hospitalization, clinic) following vaccination. The participants could report multiple adverse events on each day after vaccination. If a participant reported an on-going adverse event for more than one day, this was counted as one adverse event.

2.3. Statistical analysis

The number of non-serious and serious adverse events reported in the CVMS and their reporting rates per 100,000 doses administered were analyzed by sex, age group (18–64 and ≥65 years), and vaccine dose. The types of symptoms and signs were described with the reporting rate per 100,000 doses in decreasing order of the number of cases reported as adverse events. The events do not indicate medically confirmed diagnoses since all adverse events reported to the CVMS are suspected cases. The number of adverse events and health conditions reported through the TMS at least once during days 0 to 7 after vaccination were analyzed by vaccine dose and age group (18–64 and ≥65 years). All survey items were assessed by the chi-square or Fisher exact test as appropriate to compare differences between two age groups. A *p*-value less than 0.05 was considered statistically significant. As data on COVID-19 status were not collected in both the CVMS and TMS, adverse events were not analyzed considering the history of COVID-19 infection in this study.

2.4. Statistical software

All analyses were conducted using SAS ver. 9.4 (SAS Institute, Cary, NC, USA).

2.5. Ethical considerations

The surveillance activity based on the CVMS was conducted by the KDCA under the government regulations; the study was not subject to institutional review board approval. The study based on the TMS was exempted from review by the Public Institutional Review Board designated by the Ministry of Health and Welfare (No. P01-202206-01-033).

3. Results

3.1. Adverse events reported in the COVID-19 Vaccination Management System

From February 14 to December 31, 2022, the CVMS received a total of 1,230 adverse events reports among persons aged 18 years and over after primary and booster doses of the Novavax COVID-19 vaccination (Table 1); 1,158 (94.1%) were non-serious and 72 (5.9%) were serious. Serious adverse events included death (16, 1.3%), suspected anaphylaxis (11, 0.9%), and others including major adverse events such as AESIs for COVID-19 vaccines (45, 3.7%). A total of 926,982 doses were administered during the study period, showing an overall reporting rate per 100,000 doses of 132.7. The reporting rate was lower after booster doses (84.0) than after dose 1 (254.6) or dose 2 (272.9); and in 65-year-olds and over (83.4) than in 18- to 64-year-olds (168.1). Among non-serious adverse events, the most commonly reported symptoms based on the reporting rate per 100,000 doses were myalgia (28.2), headache (26.2), dizziness (19.0), chest pain (18.0), and allergic reactions (17.5) (Table 2). Among serious adverse events, acute paralysis (1.4) showed the greatest reporting rate per 100,000 doses, followed by anaphylaxis including anaphylactoid reactions (1.2), and acute cardiovascular injury including myocarditis (0.8).

3.2. Adverse events reported through the text-message survey

From February 21 to April 24, 2022, a total number of participants aged 18 years and over enrolled in at least one survey on days 0 to 7 following Novavax COVID-19 vaccination was 5,020 after dose 1 and 2,885 after dose 2 (Table 3). Local and systemic adverse events after dose 1 were higher in 18- to 64-year-olds (local: 42.5%; systemic: 45.1%) than in 65-year-olds and over (local: 28.2%; systemic: 31.8%) (p<0.001). This trend was the same after dose 2, indicating a higher proportion of local and systemic adverse events in 18- to 64-year-olds (local: 70.6%; systemic: 68.3%) than in 65-year-olds and over (local: 43.6%; systemic: 41.7%) (p<0.001) (Figure 1; Table 3). Among local adverse events, injection site pain, itching, and swelling were the most frequently reported, and among systemic adverse events, fatigue or tiredness, myalgia, and headache were the most frequently reported in both age groups after either dose. More than one-tenth reported that they were limited to performing normal daily activities after dose 1 but there was no statistical difference between 18- to 64-year-olds (15.6%) and 65-year-olds and over (11.4%) (p=0.059). Meanwhile, this proportion after dose 2 was 36.1% in 18- to 64-year-olds and 15.2% in 65-year-olds and over (p<0.001) (Figure 1; Table 3). Approximately 2.5 to 3.8% of all participants visited healthcare facilities including emergency rooms, hospitalization, and clinics after either dose.

4. Discussion

The results of the TMS are consistent with the safety data reported in clinical trials [4,5] and the United States (US) [14]; adverse events following Novavax COVID-19 vaccination were more frequently reported among 18- to 64-year-olds compared to 65-year-olds and over. However, when making comparisons with a clinical trial, caution should be exercised as the TMS was based on self-reporting without being medically verified. The most common adverse events after the primary series of Novavax COVID-19 vaccination among persons aged 18 years and over were injection site pain, fatigue, myalgia, or headache and these results are similar to the safety data assessed by the US and European Medicines Agency (EMA) [14,15].

According to the CVMS, the overall reporting rate of adverse events after Novavax COVID-19 vaccination among persons aged 18 years and over was 132.7 per 100,000 doses administered. This rate was lowest compared to that reported following other COVID-19 vaccines in Korea: Janssen (588.0), AstraZeneca (543.0), Moderna (450.0), Pfizer-BioNTech (304.0) as of December 31, 2022 [16]. However, considering the difference in target populations (e.g., age) and immunization regimens (e.g., homologous or heterologous) for each vaccine administered in Korea, caution should be taken in interpreting the results. Moreover, the reporting rate per 100,000 doses of booster doses (84.0) was the lowest compared to that of dose 1 (254.6) or dose 2 (272.9); these results are similar to safety data from surveys in Australia, reporting the lowest proportion in booster doses (dose 1: 37%; dose 2: 57%; boosters: 31%) as of May 1, 2023 [17].

The total number of serious adverse events reported in the CVMS was 72 including 13 suspected cases of acute paralysis, seven suspected cases of acute cardiovascular injury, and 16 deaths. Until now, none of the death reports was evaluated to be associated with the Novavax COVID-19 vaccine based on epidemiological investigation results and medical records through an initial review performed by provincial rapid response teams. Reviewing seven suspected cases of acute cardiovascular injury, the number of cases was four in females and three in males with a median age of 44 (18 to 86) years. The number of cases after dose 1 (4; 57.1%) was higher than after booster doses (2; 28.6%) or dose 2 (1; 14.3%), and suspected cases of myocarditis were four and others were three. In clinical trials, four to five myocarditis and/or pericarditis cases with a temporal relationship to the vaccine were detected among 41,546 Novavax COVID-19 vaccine recipients aged 16 years and over, and global post-authorization surveillance identified 35 reports (males: 20; females: 15) of myocarditis and/or pericarditis among 744,235 Novavax COVID-19 vaccine recipients with a median age of 34 years. However, it was determined that myocarditis rates and vaccine effectiveness for the Novavax COVID-19 vaccine cannot be compared directly based on available data, highlighting the importance of post-authorization monitoring for both vaccine effectiveness and safety [18].

Reviewing 13 suspected cases of acute paralysis, the number of cases was seven in females and six in males with a median age of 52 (37 to 77) years. The number of cases after booster doses (7; 53.8%) was greater than after dose 1 (3; 23.1%) or dose 2 (3; 23.1%), and the majority of suspected cases were facial paralysis (10; 76.9%) followed by general paralysis (3; 23.1%). Although very few cases of facial paralysis including Bell's palsy following mRNA-based or viral vector COVID-19 vaccination were reported in clinical trials [19,20] and a systematic review [21], no clear evidence that these cases are associated with the COVID-19 vaccines has been identified. Furthermore, the disproportionality analysis using the pharmacovigilance database concluded that mRNA-based COVID-19 vaccines did not show an increased risk of facial paralysis compared to other viral vaccines [22]. In this respect, although the information on the recently authorized protein subunit-based COVID-19 vaccine is currently scarce, this study supports that the benefit of Novavax COVID-19 vaccination outweighs any potential risk and recommends continuing vaccine safety surveillance to provide additional information [14]; therefore, further study would be required for conclusive evidence on the Novavax COVID-19 vaccine-associated serious adverse events such as myocarditis and facial paralysis, providing medically confirmed diagnoses for suspected cases in Korea.

We acknowledge that this study has some limitations. First, all adverse events were not medically confirmed for an accurate diagnosis as the data were based on suspected cases reported following COVID-19 vaccination; therefore, the results do not indicate causality. Second, the results might have been subject to underestimation since adverse events reported in the CVMS are based on individuals who visited medical institutions; and on-going events from the TMS during days 0 to 7 after vaccination were counted as one event respectively. Third, the analysis did not take into consideration the history of COVID-infection, which may have affected the frequency and severity of adverse events. Fourth, the findings cannot be generalized to the entire population in Korea as the text messages were sent to Novavax

COVID-19 vaccine recipients with smartphones during a particular period. In conclusion, we demonstrated no major safety issues and fewer adverse events in 65-year-olds and over compared to 18- to 64-year-olds following the Novavax COVID-19 vaccination in Korea based on two national vaccine safety data.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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287 **Table 1.** Characteristics of adverse events reported to the CVMS among persons aged 18 years and over after
288 Novavax COVID-19 vaccination, Republic of Korea, February 14 to December 31, 2022

Variable	Number of doses administered	Adverse events[a]					
		Total	Non-serious adverse events[b]	Serious adverse events[c]			
				Sub-total	Death	Anaphylaxis	Others[d]
Total	926,982	1,230 (132.7)	1,158 (124.9)	72 (7.8)	16 (1.7)	11 (1.2)	45 (4.9)
Dose 1	138,264	352 (254.6)	328 (237.2)	24 (17.4)	6 (4.3)	5 (3.6)	13 (9.4)
Dose 2	113,955	311 (272.9)	300 (263.3)	11 (9.7)	1 (0.9)	3 (2.6)	7 (6.1)
Boosters[e]	674,763	567 (84.0)	530 (78.5)	37 (5.5)	9 (1.3)	3 (0.4)	25 (3.7)
Sex							
Male	440,822	464 (105.3)	431 (97.8)	33 (7.5)	9 (2.0)	2 (05)	22 (5.0)
Dose 1	60,733	131 (215.7)	124 (204.2)	7 (11.5)	2 (3.3)	1 (1.6)	4 (6.6)
Dose 2	49,301	103 (208.9)	97 (196.8)	6 (12.2)	1 (2.0)	1 (2.0)	4 (8.1)
Boosters	330,788	230 (69.5)	210 (63.5)	20 (6.0)	6 (1.8)	0	14 (4.2)
Female	486,160	766 (157.6)	727 (149.5)	39 (8.0)	7 (1.4)	9 (1.9)	23 (4.7)
Dose 1	77,531	221 (285.0)	204 (263.1)	17 (21.9)	4 (5.2)	4 (5.2)	9 (11.6)
Dose 2	64,654	208 (321.7)	203 (314.0)	5 (7.7)	0	2 (3.1)	3 (4.6)
Boosters	343,975	337 (98.0)	320 (93.0)	17 (4.9)	3 (0.9)	3 (0.9)	11 (3.2)

Age (years)							
18–64	539,698	907 (168.1)	868 (160.8)	39 (7.2)	2 (0.4)	11 (2.0)	26 (4.8)
Dose 1	114,212	314 (274.9)	297 (260.0)	17 (14.9)	0	5 (4.4)	12 (10.5)
Dose 2	93,001	272 (292.5)	264 (283.9)	8 (8.6)	1 (1.1)	3 (3.2)	4 (4.3)
Boosters	332,485	321 (96.5)	307 (92.3)	14 (4.2)	1 (0.3)	3 (0.9)	10 (3.0)
≥65	387,284	323 (83.4)	290 (74.9)	33 (8.5)	14 (3.6)	0	19 (4.9)
Dose 1	24,052	38 (158.0)	31 (128.9)	7 (29.1)	6 (24.9)	0	1 (4.2)
Dose 2	20,954	39 (186.1)	36 (171.8)	3 (14.3)	0	0	3 (14.3)
Boosters	342,278	246 (71.9)	223 (65.2)	23 (6.7)	8 (2.3)	0	15 (4.4)

Data are presented as *n* (per 100,000): the reporting rate of adverse events per 100,000 doses administered.

CVMS, COVID-19 vaccination management system; COVID-19, coronavirus disease 2019.

[a]Data were based on suspected cases following COVID-19 vaccination reported by medical institutions or doctors; therefore, the results do not indicate medically confirmed diagnoses or causality between the events and the vaccines.

[b]Non-serious adverse events include common symptoms such as redness, pain, and swelling at the injection site, myalgia, fever, headache, chills, and others.

[c]Serious adverse events include death, suspected anaphylaxis, and others.

[d]Others include adverse events of special interest (AESIs), intensive care unit admission, life-threatening events, permanent disability or sequelae, and others.

[e]Boosters include dose 3 or more.

300 **Table 2.** Types of symptoms and signs reported to the CVMS among persons aged 18 years and over after Novavax
301 COVID-19 vaccination, Republic of Korea, February 14 to December 31, 2022

Symptoms and signs[a]	**Case (per 100,000)**
Non-serious adverse events (*n*=1,158)	
Myalgia	261 (28.2)
Headache	243 (26.2)
Dizziness	176 (19.0)
Chest pain	167 (18.0)
Allergic reactions	162 (17.5)
Pain, redness, or swelling at the injection site within 3 days after	127 (13.7)
Nausea	114 (12.3)
Dyspnea[b]	94 (10.1)
Itching[b]	86 (9.3)
Chills	80 (8.6)
Fever	73 (7.9)
Vomiting	53 (5.7)
Cellulitis	37 (4.0)
Abdominal pain	35 (3.8)
Diarrhea	30 (3.2)

Lymphadenitis	29 (3.1)
Arthritis	26 (2.8)
Abnormal uterine bleeding	26 (2.8)
Severe local adverse events	15 (1.6)
Abscess at the injection site	4 (0.4)
Severe adverse events (*n*=72) including reports of death	
Acute paralysis[c]	13 (1.4)
Anaphylaxis[d]	11 (1.2)
Acute cardiovascular injury[e]	7 (0.8)
Vaccine-associated enhanced disease	6 (0.6)
Thrombosis[f]	3 (0.3)
Guillain-Barre syndrome	3 (0.3)
Encephalopathy or encephalitis	3 (0.3)
Acute liver injury	1 (0.1)
Acute reactive arthritis	1 (0.1)
Acute kidney injury	1 (0.1)
Multisystem inflammatory syndrome	1 (0.1)
Anosmia or ageusia	1 (0.1)

Convulsions or seizures	1 (0.1)

Data are presented as *n* (per 100,000): the reporting rate of adverse events per 100,000 doses administered.

CVMS, COVID-19 vaccination management system; COVID-19, coronavirus disease 2019.

[a]Data were based on suspected cases following COVID-19 vaccination reported by medical institutions or doctors; therefore, the results do not indicate medically confirmed diagnoses or causality between the events and the vaccines.

[b]Dyspnea and itching were reported from March 10, 2022.

[c]Acute paralysis includes facial paralysis and general paralysis

[d]Anaphylaxis includes anaphylactoid reactions.

[e]Acute cardiovascular injury includes myocarditis and others.

[f]Thrombosis includes phlebothrombosis, cerebral venous sinus thrombosis, and thrombosis with thrombocytopenia syndrome.

313 **Table 3.** Adverse events and health conditions reported among persons aged 18 years and over following Novavax
314 COVID-19 vaccination, Republic of Korea, February 21 to April 24, 2022

Events[a)]	Dose 1 (*n*=5,020)			Dose 2 (*n*=2,885)		
	18–64 years (*n*=4,740)	≥65 years (*n*=280)	*p*-value[b]	18–64 years (*n*=2,681)	≥65 years (*n*=204)	*p*-value[b]
Local adverse events	2,013 (42.5)	79 (28.2)	<0.001	1,894 (70.6)	89 (43.6)	<0.001
Pain	1,559 (32.9)	49 (17.5)	<0.001	1,560 (58.2)	66 (32.4)	<0.001
Redness	73 (1.5)	2 (0.7)	0.441	487 (18.2)	23 (11.3)	0.013
Swelling	173 (3.6)	5 (1.8)	0.101	695 (25.9)	24 (11.8)	<0.001
Itching	402 (8.5)	10 (3.6)	0.004	1,029 (38.4)	52 (25.5)	<0.001
Urticaria	60 (1.3)	1 (0.4)	0.260	105 (3.9)	6 (2.9)	0.485
Others	809 (17.1)	46 (16.4)	0.782	442 (16.5)	31 (15.2)	0.631
Systemic adverse events	2,136 (45.1)	89 (31.8)	<0.001	1,831 (68.3)	85 (41.7)	<0.001
Fever	552 (11.6)	24 (8.6)	0.117	707 (26.4)	25 (12.3)	<0.001
Chills	431 (9.1)	12 (4.3)	0.006	696 (26.0)	16 (7.8)	<0.001
Headache	990 (20.9)	42 (15.0)	0.018	1,000 (37.3)	26 (12.7)	<0.001
Joint pain	312 (6.6)	14 (5.0)	0.297	424 (15.8)	10 (4.9)	<0.001
Myalgia	1,014 (21.4)	34 (12.1)	<0.001	1,188 (44.3)	48 (23.5)	<0.001
Fatigue or tiredness	1,253 (26.4)	48 (17.1)	0.001	1,291 (48.2)	43 (21.1)	<0.001

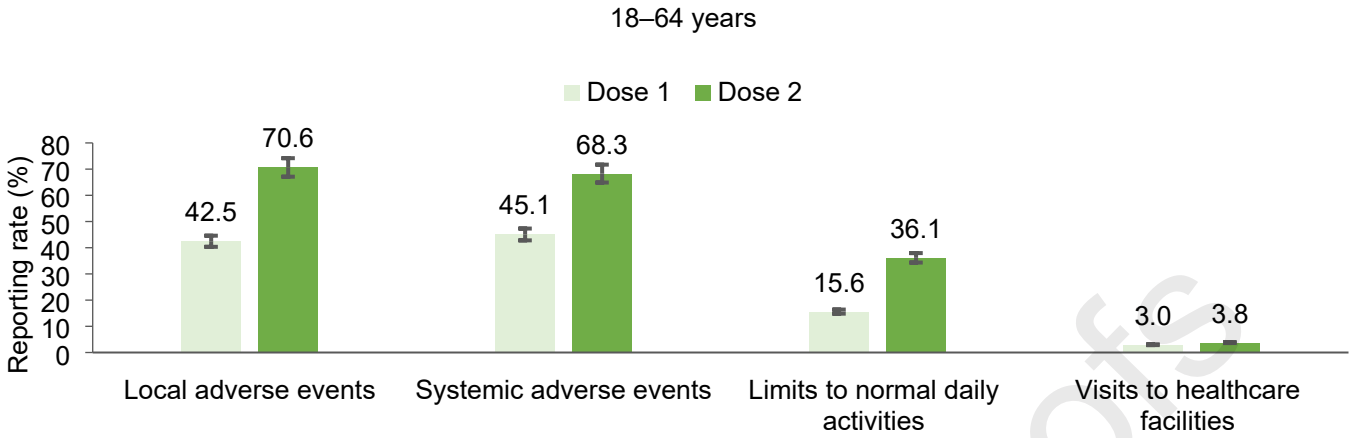
Nausea	383 (8.1)	8 (2.9)	0.002	307 (11.5)	7 (3.4)	<0.001
Vomiting	39 (0.8)	1 (0.4)	0.725	35 (1.3)	0	0.172
Diarrhea	198 (4.2)	9 (3.2)	0.431	132 (4.9)	3 (1.5)	0.024
Abdominal pain	128 (2.7)	5 (1.8)	0.354	101 (3.8)	1 (0.5)	0.015
Rash	10 (0.2)	0	0.442	14 (0.5)	0	0.618
Armpit tenderness	295 (6.2)	10 (3.6)	0.071	389 (14.5)	22 (10.8)	0.142
Chest pain	325 (6.9)	9 (3.2)	0.018	174 (6.5)	4 (2.0)	0.010
Dizziness	548 (11.6)	19 (6.8)	0.014	427 (15.9)	21 (10.3)	0.032
Others	489 (10.3)	23 (8.2)	0.259	304 (11.3)	19 (9.3)	0.377
Limits to normal daily activities	740 (15.6)	32 (11.4)	0.059	969 (36.1)	31 (15.2)	<0.001
Visits to healthcare facilities	141 (3.0)	10 (3.6)	0.323	102 (3.8)	5 (2.5)	0.324
Emergency room	23 (0.5)	1 (0.4)	1.000	6 (0.2)	0	1.000
Hospitalization	2 (0.0)	0	1.000	2 (0.1)	0	1.000
Clinic	127 (2.7)	9 (3.2)	0.592	98 (3.7)	5 (2.5)	0.372

Data are presented as *n* (%): the percentage of respondents who reported adverse events and health conditions at least once during days 0 to 7 after vaccination.

COVID-19, coronavirus disease 2019.

[a]Participants could report multiple adverse events on each day; if a participant reported an on-going adverse event for more than one day, this was counted as one adverse event.

[b]Chi-square or Fisher exact test was conducted as appropriate.



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